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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,276	12/03/2003	Wasimul Haque	12695.13USD2	1586

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EXAMINER	
LEWIS, AMY A	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,276	HAQUE ET AL.	
	Examiner	Art Unit	
	Amy A. Lewis	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/29/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/29/2008 has been entered.

Applicants' arguments, filed 4/29/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5) Claims 1 and 5-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabled for treating cerebral ischemia or ischemic stroke with P5P, does not reasonably provide enablement for prevention of cerebral ischemia or ischemic stroke.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

The nature of the invention & breadth of the claims:

The claims are directed to methods of treating as well as preventing cerebral ischemia or ischemic stroke with pyridoxal-5'-phosphate (also referred to as PLP). Treatment as well as the therapeutically effective amount are inclusive of preventing as well as prophylactic usage (see page 5, line 30, through page 6, line 16 of the specification).

The relative skill of those in the art:

The relative skill of those in the art is high, generally that of an M.D. or M.D./Ph.D.

The state of the prior art & the predictability/unpredictability of the art:

The state of the art regarding the treatment of stroke and the *in vivo* regeneration of neurons for the treatment of stroke is complex as well as unpredictable. As reviewed by Cheng et al. ("Neuroprotection for ischemic stroke," *NeuroRx* Jan 2004, Vol. 1, 36-45), there are a wide variety of factors involved in the pathology of stroke and the mechanism of nerve regeneration. Cheng et al. state the following:

> The concept of neuroprotection mainly came from the studies of the pathology and pathophysiology of ischemic brain injury. It has been well documented that abrupt deprivation of oxygen and glucose to neuronal tissues elicits a series of pathological cascades, leading to spread of neuronal death. Of the numerous pathways identified, excessive activation of glutamate receptors, accumulation of intracellular calcium cations, abnormal recruitment of inflammatory cells, excessive production of free radicals, and initiation of pathological apoptosis are believed to play critical roles in ischemic damage, especially in the penumbral zone. (see page 36).

The state of the art regarding treatment of stroke is also very unpredictable, see Table 1 (on page 37) which summarizes a wide variety of clinical trials and the varied (poor) outcomes. Chen et al. even specifically state the "neuroprotective benefits from the laboratory bench to the emergency room have not been successful" (p. 36).

The presence or absence of working examples:

Applicants demonstrate smaller infarct volume and improvement and improved scores on the neurological deficit evaluation following treatment with PLP in rat who have suffered cerebral ischemia. See Example 34 pages 50-53.

However, Applicants have not demonstrated prevention of ischemic damage.

The specification does not enable a person skilled in the art to which is pertains to make or use the invention commensurate in scope with the claims. Applicants have failed to provide

guidance and information sufficient to allow the skilled artisan to ascertain that the present active agent (PLP) is effective for preventing cerebral ischemia or ischemic stroke. The limited disclosure for smaller infarct volume and better neurological scores in rats who have suffered an ischemic stroke by administering PLP is noted but does not support a claim of prevention. Prevention of cerebral ischemia and stroke, according to Applicant's disclosure and the state of the art, cannot be accomplished with any reasonable certainty or without undue burden of experimentation.

For inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, as is the case for prevention of ischemia, including cerebral ischemia and ischemic stroke, more evidence is required to show possession (MPEP § 2163). Therefore, absent a reasonable *a priori* expectation of success prevention of ischemia by administration of PLP, the practice of the invention, as it is claimed in its current scope, would require an undue amount of experimentation because the specification provides inadequate guidance to do otherwise.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 1 and 5-11 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6043259.

Dhalla et al. teach pyridoxal-5'-phosphate for treating ischemia reperfusion injury in various organs and cardiovascular disease in dosages ranging from 0.5 to 100 mg/kg via enteral and parenteral administration (see col. 1 line 60 – col. 2 line 42 and claim 4). The route of administration of the Dhalla et al. treatment is the same as that currently claimed, i.e., parenteral (see col. 4, lines 30-35), therefore any treatment efficacy resultant from the practice of the instant invention would be the same as is present in that taught by Dhalla et al., including the active agent being present in the cerebral ischemic sites. Accordingly, ischemia present in the brain is also included in the teaching of treating ischemia in general wherever it occurs.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that

the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 1 and 5-11 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6043259.

Dhalla et al. is applied as above. Further, as reference defines ischemia and resulting injury as the following (see col. 1 lines 42-57):

> Ischemia is defined by an organ or a part of the body failing to receive a sufficient blood supply. An organ that is deprived of a blood supply is said to be hypoxic. An organ will become hypoxic even when the blood supply temporarily ceases, such as during a surgical procedure or during temporary artery blockage. Ischemia leads to structural and functional abnormalities, such as arrhythmias, cell death and ventricular remodeling. When the organ affected is the heart this condition is known as ischemic heart disease.
>
> When blood flow resumes to an organ after temporary cessation, this is known as ischemic reperfusion of the organ. Ischemic reperfusion to an organ also leads to injury of the organ by producing structural and functional abnormalities in the tissue of the organ. Conditions observed with ischemia reperfusion injury include neutrophil infiltration, and necrosis.

Accordingly, it is obvious that treatment of ischemia in general as taught by Dhalla et al. would also treat ischemia present in the brain, including that resulting from stroke. As the same compound is being administered via the same method, i.e., to the same patient population at the same dosage.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 1 and 5-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-20 of copending Application No. 10/974718. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to the treatment of cerebroovascular disease (i.e., stroke) with the compound pyridoxal-5'-phosphate.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2) Claims 1 and 5-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30 and 36 of copending

Application No. 10/549505. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to the treatment of cerebrovascular disease and ischemia (i.e., stroke) with the compound pyridoxal-5'-phosphate.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3) Claims 1 and 5-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 10 of U.S. Patent No. 6867215. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to the treatment of ischemia reperfusion injury (i.e., stroke) with the compound pyridoxal-5'-phosphate.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy A. Lewis whose telephone number is 571-272-9032. The examiner can normally be reached on Monday-Friday 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amy A Lewis/

Examiner, Art Unit 1614

/Ardin Marschel/
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